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(54) Title: CONTROLLED DELIVERY OF BISPHOSPHONATES

(57) Abstract

A method for controlled delivery of bisphosphonates for treatment of osteoporosis, Paget's disease and other bone diseases is described. The method involves the use of an implantable device, which delivers pharmaceutically effective amounts of the bisphosphonates in the absence of many of the side effects of oral dosing.

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CONTROLLED DELIVERY OF BISPHOSPHONATES

FIELD OF THE INVENTION

This invention relates generally to the controlled delivery of drugs and more specifically to the delivery of drugs from long term polymeric implanted devices.

BACKGROUND OF THE INVENTION

Bisphosphonates are chemical compounds that have C-P bonds, especially P-C-P bonds. Some bisphosphonates that have been commercialized include: alendronate, clodronate, pamidronate and etidronate. Others such as cimadronate, ibandronate, neridronate, olpadronate, tiludronate, risedronate, and zoledronate are in different stages of pharmaceutical development.

Due to the affinity that bisphosphonates exhibit in binding to bone, they have been used to treat bone diseases such as osteoporosis, Paget's disease, hypercalcemia and bone cancer. Osteoporosis is a disease where reduction in bone mass takes place and specifically when that bone mass is 2.5 standard deviations less than that of young adults. This bone-brittling disease affects 20 million Americans, with only about 2 million currently being treated.

Bisphosphonates have been used to treat both post-menopausal osteoporosis as well as corticosteroid-induced osteoporosis and have been shown to increase both the mineral density, as well as the mechanical strength of bone. For example, the lumbar spine density of patients with osteoporosis was increased by 7% over a two year period when patients were treated with 150 mg pamidronate orally, while the lumbar spine density of the placebo group decreased by 1% over the baseline [L. Reid, et al., J. Clin. Endocrinol. Metab., 79: 1595 (1994)]. Etidronate has also been used to treat calcification, i.e, deposition of calcium phosphate in areas that are not normally calcified (soft tissue). Bisphosphonates therefore may have use in the prevention of kidney stones, dental calculi, ectopic bone formation and calcification of heart valves. Other applications for bisphosphonates include treatment for Paget's disease (localized foci of increased bone turnover), osteolytic tumor bone diseases and non-tumor induced hypercalcemia.

The oral dose bioavailability of bisphosphonates in animals as well as humans is low, between 1% and 10% [H. Fleisch., Bisphosphonates in Bone Disease, The Parthenon Publishing Group, New York, p.57 (1995)]. It is generally lower for the more potent bisphosphonates such as amino derivatives which are delivered in lower amounts. Relative to an intravenous reference dose, the mean oral bioavailability of alendronate in women was 0.7% for doses ranging from 5 to 40 mg when administered after an overnight fast and two hours before a standardized breakfast [Merck package insert for Fosamax (alendronate sodium tablets)]. The bioavailability decreases further if the drug is given with meals, especially when calcium, iron or other multivalent cations are present. Oral delivery of bisphosphonates is never administered during mealtimes or with orange juice, coffee, milk or iron supplements. With alendronate, bioavailability was reduced by 60% when given with coffee or orange juice. Bioavailability was negligible when alendronate was delivered up to two hours after a standardized breakfast [Fosamax package insert].

Bisphosphonates can also cause esophageal irritation to the upper gastrointestinal mucosa. Esophageal adverse reactions such as esophagitis, esophageal ulcers, and esophageal erosions with bleeding have been reported in patients receiving treatment with Fosamax [Fosamax package insert].

With Fosamax, rare events of gastric and duodenal ulcers, some severe and with complications, have also been reported. Additionally, oral bisphosphonates have been known to produce other gastrointestinal side effects such as nausea, dyspepsia, vomiting, gastric pain and diarrhea.

There are also undesirable side effects upon intravenous (i.v.) delivery of bisphosphonates, including deposition in other organs, mostly the liver and spleen. The deposition is proportionally greater when large amounts of the compounds are given [H. Fleisch, Bisphosphonates in Bone Disease, The Parthenon Publishing Group, New York p. 58 (1995)]. This extraosseous deposition appears to be due to formation of metal complexes or aggregates after too rapid of an intravenous injection. The formation of aggregates in the blood possibly explains the renal

failure that can ensue. When the aggregates are formed with calcium, a decrease in ionized calcium can take place resulting in hypocalcemia, an acute toxicity which needs to be rapidly corrected. Therefore, when bisphosphonates are administered intravenously, the rate of infusion will have to be carefully controlled and monitored.

In healthy volunteers the bisphosphonates that are not deposited in the bone are rapidly excreted in the urine. However, when renal insufficience is present, the excretion cannot take place efficiently, so increasing amounts of drug are present in the plasma, kidney, spleen, and tibia. Thus, bone absorption may increase. Fosamax is not recommended for patients with severe renal insufficiency [Fosamax package insert].

For some bisphosphonates, e.g., etidronate, the dosage required to decrease bone absorption is similar to the dose causing inhibition of bone calcification or mineralization. This can cause osteomalacia, where the amount of bone is normal but the percent of mineral is reduced causing softening of the bones, which then allows bones to also fracture. Osteomalacia is distinct from osteoporosis, because in osteoporosis the amount of bone is decreased but the percent mineral is normal.

When large doses of bisphosphonates are delivered (i.v. delivery) they can form metal aggregates which deposit on non-calcified tissues and can cause renal failure and hypocalcemia. In patients with renal insufficiency, bisphosphonates are contraindicated because bone absorption can increase in a non-predictable fashion.

What are needed are methods for delivery of bisphosphonates which avoid the undesirable side effects associated with current oral medications and also which avoid the formation of metal aggregates caused by high dose delivery methods.

SUMMARY OF THE INVENTION

The present invention provides a drug delivery device useful in a method for controlled delivery of bisphosphonates to a patient over an extended time period. This method provides a pharmaceutically effective amount of bisphosphonates, while avoiding metal aggregation sometimes associated with prior art intravenous

administration of bisphosphonates and the undesirable gastrointestinal side effects associated with oral delivery.

Thus, in one aspect, the present invention provides an implantable drug delivery device containing bisphosphonate. Suitably, the device delivers at least one bisphosphonate at a daily dose that is less than 50% of its oral dose for an extended period of time, e.g., three to twelve months. In one particularly desirable embodiment, the device is a hydrogel polymer material and the bisphosphonate is alendronate.

In another aspect, the present invention provides a method of delivering bisphosphonate to a patient. This method involves implanting the patient with a drug delivery device as described herein. Desirably, the bisphosphonates are released at zero or near zero order kinetics and the drug delivery device is a biodegradable polymer.

Other aspects and advantages of the invention will be readily apparent from the detailed description of the invention.

Detailed Description of the Invention

The invention provides a device useful in a method for treating veterinary and human patients with bone diseases by delivering bisphosphonates. This device is particularly well suited to treatment of such chronic illnesses as osteoporosis and Paget's disease, avoids the gastrointestinal problems associated with oral medications containing bisphosphonates and provides a continuous low dosage which avoids metal aggregate formation, renal failure and hypocalcemia. The reduction in dosage provided by the use of the present invention is also effective in eliminating the problems associated with inhibition of bone mineralization.

Thus the present invention pertains to the parenteral delivery of low amounts of bisphosphonates in a continuous, slow and controlled administration. More specifically, the present invention pertains to an implantable device which delivers over an extended period of time from three months to one year, a bisphosphonate at

a daily dose which is from 0.5% to 50%, and preferably 0.5% to 25%, and most preferably, 0.5% to 10%, of current oral doses of these compounds.

Bisphosphonates

One of skill in the art can readily select the desired bisphosphonate for use in the device and method of the invention. Such bisphosphonates may be produced using conventional methods or may be purchased commercially. For example, alendronate ((4-amino-1-hydroxybutylidene)-bis-phosphonate) is commercially available from Gentili and Merck Sharp & Dohme. A suitable daily oral of alendronate dose for a human or non-human animal of about 80 kg (hereinafter adult) is in the range of 20 to 40 mg. Cimadronate ([(cycloheptylamino)-methylene]bis-phosphonate) is available from Yamanouchi. Clodronate ((dichloromethylene)-bis-phosphonate) is available from Astra and Boehringer Mannheim, among others, and is typically administered in an amount of 400 to 1660 mg/daily adult oral dose. EB-1053 ([1-hydroxy-3-(1-pyrrolidinyl)-propylidene]bis-phosphonate is available from Leo. Etidronate, (1-Hydroxyethylidene)-bis-phosphonate, is available from Procter & Gamble and Gentili and is typically administered at 400 to 800 mg/ daily adult oral dose. Ibandronate, [1-Hydroxy-3-(methylpentylamino)propylidene]bis-phosphonate is available from Boehringer Mannheim. Neridronate, (6-Amino-1-hydroxyhexylidene)bis-phosphonate, is available from Gentili. Olpadronate, [3-(Dimethylamino)-1-hydroxypropylidene]bis-phosphonate, is available from Gador and is typically administered at 200 mg/daily adult oral dose. Pamidronate, (3-Amino-1-hydroxypropylidene)bis-phosphonate, is available from Ciba-Geigy and Gador and is typically administered at a daily adult oral dose of 250 to 300 mg. Risedronate, [1-Hydroxy-2-(3-pyridinyl)-ethylidene]bis-phosphonate, is available from Procter & Gamble. Tiludronate, [[(4-Chlorophenyl)thio]-methylene]bis-phosphonate, is available from Sanofi. YH 529, [1-Hydroxy-2-imidazo-(1,2-a)pyridin-3-ylethylidene]bis-phosphonate is available from Yamanouchi. Zoledronate, [1-

Hydroxy-2-(1H-imidazol-1-yl)ethyliden]bis-phosphonate, is available from Ciba-Geigy.

The device and method of the invention are particularly well suited to extended delivery of bisphosphonates at a level which is lower than the oral dose. Thus, doses of the bisphosphonate or combinations thereof, selected for delivery can readily be selected by one of skill in the art. Generally, the doses are 0.5% to 50%, preferably, 0.5% to 25%, and most preferably 0.5% to 10%, of the oral doses identified above. However, the dose may be adjusted as needed, depending upon a number of factors, including the age, weight, and condition of the veterinary or human patient. For example, doses in the range of 1% to 5% of oral doses, or other alternative doses, may be desirable. Typically, the doses delivered by the method of the invention are also lower than current intravenous doses of bisphosphonate.

Optionally, the delivery devices may contain more than one bisphosphonate and/or may contain additional ingredients. For example, it may be desirable to administer a bisphosphonate in combination with a vitamin compound (e.g., Vitamin D and analogs thereof), calcium, an anti-inflammatory agent (including, but not limited to corticosteroids), prostaglandin inhibitors, calcitonin, or another active agent.

Drug Delivery Devices

In various embodiments, the novel drug delivery device of the invention is designed for implantation into the body of the animal to which the bisphosphonate formulation is to be delivered. The drug delivery devices of the invention are desirably implants containing bisphosphonate in a reservoir, optionally together with another active agent and/or a pharmaceutically acceptable carrier. Such reservoir devices may be composed of hydrophobic or hydrophilic polymers, co-monomers, metals, or other suitable materials. Alternatively, the drug delivery devices may be hydrogels, or other polymeric or co-monomer materials, made up of a matrix having the bisphosphonates and any other optional active agents or carriers interspersed throughout. Preferably, the bisphosphonates are dispersed homogeneously

throughout the matrix. Yet other suitable implants are known to those of skill in the art and may be readily selected.

The novel implant drug delivery devices of the invention, in a preferred aspect, are highly useful in the delayed/sustained and the immediate/sustained release of bisphosphonates to animals, e.g., humans, sheep, dogs, cats, turkeys, cattle, etc. "Delayed/sustained release" is defined as delaying the release of an active agent until after placement in a delivery environment, followed by a sustained, preferably zero-order, release of the agent at a later time. Currently, this type of release is preferably achieved using a hydrogel delivery device, which may be implanted in a dry or partially hydrated state. Thus, the release of an active agent may be delayed for several weeks. "Immediate/sustained release" is defined as the commencement of the release of bisphosphonate or other active agent immediately or soon thereafter after placement in a delivery environment, followed by sustained release of the active agent. The bisphosphonates will be present in the delayed/sustained release compositions in varying amounts, depending upon the effect desired.

The amount of bisphosphonates and any other agents employed in the drug delivery devices of the invention will depend not only on the desired daily dose but also on the number of days that dose level is to be maintained. While this amount can be calculated empirically, the actual dose delivered is also a function of any interaction with materials and the carrier, if employed in the device.

Thus, the drug delivery device may contain a pharmaceutically acceptable carrier which may be in the form of suspending media, solvents, aqueous systems, and solid substrates or matrices. These carriers are known to those of skill in the art and are not intended to be a limitation on the present invention.

For example, suspending media and solvents useful as the carrier include, for example, oils such as silicone oil (particularly medical grade), corn oil, castor oil, peanut oil and sesame oil; condensation products of castor oil and ethylene oxide combining about 30 to 35 moles of ethylene oxide per mole of castor oil; liquid glyceryl triesters of a lower molecular weight fatty acid; lower alkanols; glycols;

polyalkylene glycols. The aqueous systems include, for example, sterile water, saline, dextrose, dextrose in water or saline, and the like. The presence of electrolytes in the aqueous systems may tend to lower the solubility of the bisphosphonate in them. The solid substrates or matrices include, for example starch, gelatin, sugars (e.g. glucose), natural gums (e.g. acacia, sodium alginate, carboxymethyl cellulose), and the like. The carrier may also contain adjuvants such as preserving, stabilizing, wetting and emulsifying agents, and the like.

In one suitable embodiment, hydrogels are suited as implantable delivery vehicles for use in delivery of bisphosphonates according to the present invention. One particularly desirable hydrogel is prepared by mixing about 60 weight percent to about 95 weight percent comonomers, at least one of which is hydrophilic, and sufficient amounts of a crosslinker and a liquid diffusion enhancer which is miscible with the comonomers, to yield a homogenous copolymer hydrogel having the equilibrium water content (EWC) value in the range from about 20% to about 85%. Most preferably, the polymerizable liquid mixture contains about 1 weight percent to about 50 weight percent diffusion enhancer which may be readily selected from among C1-C4 alkyl alcohol, allyl alcohol, tetrahydrofuryl alcohol, cyclohexyl alcohol, diethylene glycol, polyethylene glycols, glycerol, acetone, ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, glyceryl isopropylidene ether dioxane, tetrahydrofuran; ethyl acetate; dimethyl sulfoxide; water, and mixtures thereof. The crosslinker and comonomers may be readily selected by one of skill in the art. This hydrogel, as well as details on its preparation, are provided in preferred hydrogel is described in co-pending International Patent Application Number PCT/US00/01664, filed January 26, 2000 for "HYDROGEL COMPOSITIONS USEFUL FOR THE SUSTAINED RELEASE OF MACROMOLECULES AND METHODS OF MAKING SAME". Other suitable hydrogels may be readily selected by one of skill in the art. See, e.g., US 5,266,325; US 4,959,217; and US 5,292,515.

The hydrating liquid useful in the hydrogels used in the invention is typically a liquid simulating the environment in which the active compound will be released,

e.g., body fluid, sterile water, tear fluid, physiological saline solution, phosphate buffer solution, and the like. While liquids other than water are useful as the hydrating liquid, the degree to which a hydrophilic membrane is hydrated is referred to as its "water content".

In another suitable embodiment, the implants may be in the form of an osmotic pump, such as described by Alza [see, e.g., U. S. Patent No. 4,285,987 and U. S. Patent No. 5,273,752] or Merck [see, e.g., European Patent No. 314,206], among others. In another example, the implant device may be composed of a hydrophobic membrane material, such as ethylenemethacrylate (EMA) and ethylenevinylacetate (EVA). Other suitable implant delivery devices include bioresorbable polymer systems [see, e.g., International Patent Application No. WO98/44964, Bioxid and Cellomeda; U. S. Patent No. 5,756,127 and U. S. Patent No. 5,854,382]. Suitable bioresorbable implant devices have been described in the literature and may be composed of, for example, polyesters, polyanhydrides, or lactic acid/glycolic acid copolymers [see, e.g., U. S. Patent No. 5,817,343 (Alkermes Inc.)].

Regardless of whether the delivery device is composed of a hydrogel, EVA/EMA polymer, bioresorbable material, metal or other material, the devices useful in the invention(s) provide sustained release of bisphosphonates over extended periods of time. This time period may range from a month to a year or several years, depending on the desired administration regimen. Preferably, the bisphosphonates will be released in daily doses, over a period of about 1 week or longer, and preferably over a period of about three months to one year, it being understood that this time factor is a variable depending on the rate-releasing membrane of choice, its interconnecting pore structure, the bisphosphonates of choice, the solubility of the active compound(s) in the liquid medium, and other considerations well known to those skilled in the art.

Methods for determining the release profile (i.e., delay time, release rate and duration) of a bisphosphonate formulation from the delivery device of the invention

are well known, and include use of the Fick's First Law of Diffusion. See, e.g., US Patent 5,266,325, which is incorporated herein by reference.

Where the delivery device is composed of a hydrogel, it may be prepared such that the hydrogel forms the walls of a cavity which contain the active agent. A predetermined amount of at least one bisphosphonate per se or an admixture with an inert, non-toxic material or as a suspension in a non-toxic material or as a suspension in a non-toxic medium, e.g., medical grade silicone oil, is introduced into the cavity to partially fill the core. The void in the core is thereafter sealed to prevent leakage into or out of the vesicle. Preferably this can be accomplished by introducing sufficient polymerizable material into the void to cover the layer of inert material or to substantially or completely fill the void and thereafter effecting a polymerization reaction to form a plug of water-swellable, water-insoluble polymer which seals the opening of the vesicle. The hydrophilic polymer plug, upon maximum hydration, will have an equilibrium water content value of the hydrophilic vesicle. Using polymerizable material comprising ethylenically unsaturated monomer(s) and desirably crosslinking agent(s), a polymer plug grafted to the inner surface of the vesicle can be obtained.

In a currently desired embodiment, hydrophilic cartridges are prepared by the rotational casting of polymerizable material in a tubular mold, as described in US Patent 5,266,325 and 5,292,515, which are incorporated herein by reference. Briefly, the internal radius of the tube is approximately 1.2 to 1.3 mm, and may be larger. The tube is rotated about its longitudinal axis which is maintained parallel to the ground. Rotational speeds are of the order of 2150 rpm, though greater or lesser speeds could be used, e.g., 1000 rpm or less to 3000 rpm and more. The tubes are fabricated of polyethylene, polypropylene, glass, or other suitable materials. When the polymerizable mixture within the spinning tube stabilizes to the predetermined shape, U.V. light at a distance of less than one foot is then directed at the spinning tube for several minutes, e.g., about 7 minutes, to polymerize the mixture to the shaped product. The shaped product is cured and annealed as follows:

Thermal Cure: 60 minutes at 65° C; Postcure: 30 minutes at 95°C; Annealing: 30 minutes at 115°C with gradual cooling to about 25°C.

After shaping and polishing the closed end of the cartridge to a oval-like cylindrical profile, there is obtained small cylindrically-shaped objects having smooth, unscored cylindrical surfaces. The dimensions of the cartridges are as follows: internal radius 0.98 mm; external radius 1.3mm; length 25mm.

Smooth, unscored cylindrically-shaped objects of various lengths, e.g., up to 25 cm and longer, can also be prepared in accordance with the teachings herein. Such objects, in a hydrated state or plasticized with a non-toxic, biocompatible material, can be formed into desired shapes. A ring shape, for use as pessaries, surgical implants, etc. Yet other drug delivery devices and implant shapes may be prepared using techniques known to those of skill in the art or purchased from commercial sources.

<u>Use of Delivery Devices</u>

The invention provides a method of delivering bisphosphonates, alone or in combination with other active agents, to a veterinary or human patient in need thereof. Typically, such a patient has a bone disease or condition such as osteoporosis, Paget's disease, hypercalcemia or bone cancer.

In order to treat a patient, a delivery device as described herein can be implanted subcutaneously in an animal by perforation. Such devices are characterized by a length of 10 to 50 mm, or less (e.g., 6 to 9 mm), an external diameter of 2 to 5 mm, or less (e.g., 1.5 to 1.9 mm). The dimensions of the device (e.g., a cartridge) can vary outside of the limits stated above depending, in particular, on the medical application involved. Animals such as sheep, cows, goats, cattle, and large animals, in general, can tolerate implantation by perforation of larger dimensional drug delivery devices. Implantation can be effected by other means, e.g., open surgery.

In one embodiment, the drug delivery device is a biodegradable matrix, which is bioresorbed and eliminated from the body following completion of the

course of therapy, e.g., three to twelve months, or more. Alternatively, a selected delivery device may be removed by surgical means.

Suitably, treatment of bone conditions using the drug delivery devices of the invention may be readily combined with other therapies administered by routes other through the use of an implantable devices. For example, treatment with bisphosphonates according to the invention may be combined with other treatments or therapies, including, for example, calcium supplements, radiation, chemotherapy.

The following examples are provided to illustrate the invention and do not limit the scope thereof. One skilled in the art will appreciate that although specific reagents and conditions are outlined in the following examples, modifications can be made which are meant to be encompassed by the spirit and scope of the invention.

Examples - Preparation of Delivery Devices for Bisphosphonates

Monomeric mixtures containing one or more comonomers (listed in Table 1) and 0.5% trimethylol propane trimethacrylate were prepared. To the resulting mixtures, 0.2% benzoin methyl ether was added and dissolved. Representative samples from these formulations were cured and the resulting polymers evaluated for their hydration characteristics, expressed as % Equilibrium Water Content (% EWC). These results are also shown in Table 1.

Table 1. Polymer compositions and their % EWCs used in examples of drug delivery devices prepared for the release of bisphosphonates.

Example	% Hydroxethyl Methacrylate	% Hydroxypropyl Methacrylate	% Methyl Methacrylate	% Methacrylic Acid	% EWC
1	-	49.5	50	-	7.3
2	-	74.5	25	-	13.6
3	99.5	-	-	-	37.7
4	99.0	-	-	0.5	40.4
5	98.7	-	-	0.8	46.0
6	97.5	-	-	2.0	55.6

An implant cartridge was prepared essentially as described in US 5,266,325. More particularly, the mixture was deoxygenated by bubbling nitrogen through it for 10 minutes. To avoid premature polymerization the mixture was shielded from light. One end of a polypropylene tube (65 mm in length and d_i of 2.5 mm) was plugged with a silicone sealant; the other end of the tube was sealed with a plug made by injecting a small amount of the above mixture, which was cured under a UV lamp for 5 minutes. Using a syringe filled with said mixture, the silicone plug was punctured and the tube was filled with the mixture to a height of about 10 mm from the top. The tube was inserted in a spin casting apparatus and spun (spinning axis parallel to the ground) at about 2200 rpm. The centrifugal force created by the spinning tube caused the radially outward displacement of the mixture to assume a predetermined hollow cylindrical liquid configuration (i.e., a hollow tube of polymerizable liquid mixture). The spinning tube was then exposed to UV light for 7 minutes to polymerize the "liquid tube" to a solid hydrophilic tube (cartridge). The cartridge within the polypropylene tube was postcured for 14 hours at 65° C, followed with an additional 40 minutes at 105° C, and annealed at 116° C for 40 minutes, and then slowly cooled to 22° C.

The cartridge was ejected from the tube, inspected for defects, and cut to a length of 30 mm. There was obtained a precisely dimensional plastic cartridge fabricated of crosslinked homogeneous polymers characterized by recurring hydrophilic units. The weight of the cartridge was recorded.

This cartridge is available for filling with alendronate sodium (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate, by tightly packing it to a 20 mm height. The filled cartridge is weighed again to determine the weight of active agent bisphosphonates. The empty space of the cartridge is filled with the aforesaid monomeric mixture. Part of the cartridge containing the active agent is covered with aluminum foil. The cartridge is then placed in the lathe and spun slowly (spinning axis of cartridge parallel to ground) under a UV lamp for 5 minutes to effect polymerization of the mixture. Postcuring of the polymer plug was

effected by maintaining the cartridge at 50° C for 18 hours. The end product is an implantable drug delivery device containing bisphosphonates.

The bisphosphonates used for evaluation of these devices were etidronic acid and pamidronic acid. The solubility of etidronic acid is relatively high, therefore the delivery devices for this compound were prepared from lower % EWC polymers as shown in examples 1 and 2. Pamidronic acid was used in examples 3, 4, 5 and 6.

In vitro release rates were evaluated by placing the implants in individual glass vials containing 10 ml of physiological saline. The vials and their contents were placed in a shaker waterbath maintained at 37°C and agitated at 60 strokes/minute. The elution media were changed weekly, and assayed for their drug contents.

Detection of small amounts of bisphosphonates (microgram levels) is generally very difficult. Visual inspection of samples undergoing the elution testing indicates that the etidronic acid is being released. The colorimetric method adopted for evaluation of pamidronic acid proved to be more reliable and we were able to evaluate the release rates. The results from pamidronic elution study available to date are shown in Table 2.

Table 2. Release rates of pamidronic acid from hydrogel implants as a function of polymer Equilibrium Water Content (% EWC).

Example	Implant	Pamidronic Acid Release Rate (μg/day)				
		Week 1	Week 2	Week 3	Week 4	Week 5
3	37%	0	53	610	1,281	884
4	40%	0	245	377	1,239	4,162
5	46%	0	336	2,051	2,177	4,931
6	55%	0	1,503	3,045	1,101	1,167

All publications cited in this specification are incorporated herein by reference herein. While the invention has been described with reference to a particularly preferred embodiment, it will be appreciated that modifications can be made without departing from the spirit of the invention. Such modifications are intended to fall within the scope of the appended claims.

What is claimed is:

1. An implantable drug delivery device comprising bisphosphonate, wherein said device delivers for an extended period of time at least one bisphosphonate at a daily dose that is less than 50% of its oral dose.

2. The drug delivery device according to claim 1, where the implantable device is made out of a polymer material or metal.

3. The drug delivery device according to claim 1, where the implantable device is made from a hydrogel polymer material.

4. The drug delivery device according to claim 1, where the implantable device is a reservoir device.

5. The drug delivery device according to any of claims 1 to 4, where the bisphosphonates are released at zero or near zero order kinetics.

6. The drug delivery device according to claim 1, wherein the device is a matrix drug release device where the bisphosphonates are dispersed homogeneously throughout a polymer matrix.

7. The drug delivery device according to claim 1, wherein the implantable device is a biodegradable polymer.

8. The drug delivery device according to any of claim 1, wherein the extended period of time is 3 months.

9. The drug delivery device according to claim 1, wherein the extended period of time is up to 12 months.

10. The drug delivery device according to claim 1 where the bisphosphonate is alendronate.

11. The drug delivery device according to claim 1 where the daily dose is less than 20% of the oral dose of the bisphosphonate.

12. The drug delivery device according to claim 1 where the delivery of the bisphosphonate is by molecular diffusion.

13. A method of delivering bisphosphonate to a patient, said method comprising the step of:

implanting the patient with a drug delivery device according to any of claims 1 to 12.

14. The method according to claim 13, wherein drug delivery device is made out of a polymer material or metal.

15. The method according to claim 13, wherein the drug delivery device is made from a hydrogel polymer material.

16. The method according to claim 14, wherein the drug delivery device is a reservoir device.

17. The method according to claim 13, wherein the bisphosphonates are released at zero or near zero order kinetics.

18. The method according to claim 13, wherein the drug delivery device is a matrix drug release device where the bisphosphonates are dispersed homogeneously throughout a polymer matrix.

19. The method according to claim 13, wherein the drug delivery device is a biodegradable matrix.

20. The method according to claim 13, wherein the extended period of time is between about 3 months to 12 months.

21. The method according to claim 13, wherein the drug is alendronate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/10696

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61M 11/00; A01N 57/00; A61K 31/66
US CL : 604/93; 514/108
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/93; 514/108

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,646,134 A (YATES) 08 July 1997, see entire document.	1-12
X	WO 94/14455 A1 (MERCK & CO., INC.) 07 July 1994, see entire document.	1-12
Y	US 5,891,863 A (YATES) 06 April 1999, see entire document.	1-12
Y	WO 96/39107 A1 (MERCK & CO., INC.) 12 December 1996, see entire document.	1-12
Y,P	US 6,043,026 A (PATCHETT et al.) 28 March 2000, see entire document.	1-12
Y,P	US 5,898,038 A (YALLAMPALLI et al.) 27 April 1999, see entire document.	1-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

12 JUNE 2000

Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/10696

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 13-21
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.